

## Influences of Morphine on the Ventilatory Response to Isocapnic Hypoxia

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**Background:** The ventilatory response to hypoxia is composed of the stimulatory activity from peripheral chemoreceptors and a depressant effect from within the central nervous system. Morphine induces respiratory depression by affecting the peripheral and central carbon dioxide chemoreflex loops. There are only few reports on its effect on the hypoxic response. Thus the authors assessed the effect of morphine on the isocapnic ventilatory response to hypoxia in eight cats anesthetized with  $\alpha$ -chloralose-urethan and on the ventilatory carbon dioxide sensitivities of the central and peripheral chemoreflex loops.

**Methods:** The steady-state ventilatory responses to six levels of end-tidal oxygen tension ( $P_{O_2}$ ) ranging from 375 to 45 mmHg were measured at constant end-tidal carbon dioxide tension ( $P_{ET}CO_2$ , 41 mmHg) before and after intravenous administration of morphine hydrochloride (0.15 mg/kg). Each oxygen response was fitted to an exponential function characterized by the hypoxic sensitivity and a shape parameter. The hypercapnic ventilatory responses, determined before and after administration of morphine hydrochloride, were separated into a slow central and a fast peripheral component characterized by a carbon dioxide sensitivity and a single offset B (apneic threshold).

**Results:** At constant  $P_{ET}CO_2$ , morphine decreased ventilation during hyperoxia from  $1,260 \pm 140$  ml/min to  $530 \pm 110$  ml/min ( $P < 0.01$ ). The hypoxic sensitivity and shape parameter did not differ from control. The ventilatory response to carbon dioxide was displaced to higher  $P_{ET}CO_2$  levels, and the apneic threshold increased by 6 mmHg ( $P < 0.01$ ). The central and peripheral carbon dioxide sensitivities decreased by about 30% ( $P < 0.01$ ). Their ratio (peripheral carbon dioxide sensitivity:central carbon dioxide sensitivity) did not differ for the treatments (control =  $0.165 \pm 0.105$ ; morphine =  $0.161 \pm 0.084$ ).

**Conclusions:** Morphine depresses ventilation at hyperoxia but does not depress the steady-state increase in ventilation

due to hypoxia. The authors speculate that morphine reduces the central depressant effect of hypoxia and the peripheral carbon dioxide sensitivity at hyperoxia. (Key words: Analgesics, opioid: morphine. Anesthesia:  $\alpha$ -chloralose-urethan. Measurement techniques: carbon dioxide ventilatory response; dynamic end-tidal forcing; hypoxic ventilatory response. Receptors, chemoreceptors: central; peripheral. Species: cat. Ventilation, lung: hypoxia; hyperoxia; hypercapnia.)

IT is well known that morphine and all other opioids influence ventilatory control: Arterial carbon dioxide tension increases and the ventilatory response to inspired carbon dioxide is reduced or shifted to higher end-tidal carbon dioxide tension ( $P_{ET}CO_2$ ) values.<sup>1-5</sup> The scarce data reported on the hypoxic response indicate a reduction by opioids in awake humans.<sup>3-5</sup> The steady-state ventilatory response to hypoxia is the result of stimulation by the peripheral chemoreceptors of the carotid and aortic bodies and a central (*i.e.*, residing within the central nervous system) depressant effect.<sup>6-9</sup> This depressant effect in anesthetized cats and probably also in anesthetized humans is related to the washout of carbon dioxide at the site of the central chemoreceptors due to the increase of brain blood flow and to central inhibitory neurotransmitters.<sup>8,9</sup> The magnitude of the stimulatory and depressant components or an effect a drug has on either component cannot be determined in human or "intact" animal studies. In anesthetized animals, elaborate invasive studies (such as those using artificial perfusion of the brain stem or peripheral chemoreceptor denervation) should be performed to obtain information on these opposing ventilatory components.

In the current study, we investigated the effects of intravenous morphine on the steady-state ventilatory responses to step-wise changes in end-tidal oxygen concentration ( $P_{ET}O_2$ ) against the background of isocapnia in anesthetized cats. We also determined the ventilatory response to carbon dioxide and its central and peripheral components using the dynamic end-tidal forcing (DEF) technique.<sup>1</sup> The combination of parameters (*e.g.*, carbon dioxide sensitivities of the peripheral and

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central chemoreflex loop, apneic  $P_{ET}CO_2$  threshold, steady-state hypoxic ventilatory sensitivity, hyperoxic ventilation) obtained in one group of intact cats will allow us to infer the influence of morphine on the two hypoxia-related ventilatory components without performing invasive procedures.

## Materials and Methods

Experiments were performed on eight anesthetized female adult cats (body weight 2.6–3.8 kg). The use of the animals was approved by the Ethical Committee for Animal Experiments of the University of Leiden. Anesthesia was induced with 15 mg/kg ketamine hydrochloride given intramuscularly, followed by halothane inhalation. The right femoral vein was cannulated; 25 mg/kg  $\alpha$ -chloralose and 125 mg/kg urethan were slowly administered intravenously, and the volatile anesthetic was withdrawn. About 1 h later, an infusion of an  $\alpha$ -chloralose-urethan solution was started at a rate of 1 or 2 mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup>  $\alpha$ -chloralose and 5–10 mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> urethan. This regimen leads to conditions in which the level of anesthesia is sufficient to suppress the pain-withdrawal reflex but light enough to preserve the corneal reflex. Comparison of our studies with those of others in awake cats shows that this anesthetic regimen has little effect on the ventilatory response to elevated  $P_{ET}CO_2$  compared with the awake state and does not yield systematic changes over time (more than 6 h).<sup>10–13</sup>

The oxygen and carbon dioxide responses were studied with the DEF method before and after the administration of morphine. Because this method has been described previously, we restrict ourselves to a brief description.<sup>12</sup> In the DEF technique, the end-tidal oxygen and carbon dioxide concentrations are forced to follow a specific pattern in time (in the current study, step increases and decreases in  $P_{ET}O_2$  and  $P_{ET}CO_2$ ) independent of the changes in ventilation. This is performed by computer-driven adjustment of the inspired carbon dioxide and oxygen concentrations. The ventilatory response after a prescribed change in  $P_{ET}CO_2$  or  $P_{ET}O_2$  was assessed on a breath-by-breath basis.

To measure inspiratory and expiratory flow, the trachea was cannulated at midcervical level and connected *via* a Fleisch (Lausanne, Switzerland) number 0 flow transducer head to a T-piece of which one arm received a continuous gas flow of 5 l/min. With the aid of three computer-steered mass flow controllers (High-Tec,

Veenedaal, The Netherlands), a prescribed composition of the inspirate from pure oxygen, carbon dioxide, and nitrogen could be obtained. The respiratory fractions of oxygen and carbon dioxide were measured continuously with a fast-responding zirconium oxide cell (Jaeger, O<sub>2</sub>-test, Würzburg, Germany) and an infrared analyzer (Gould Godart MK-2 capnograph, Biltoven, The Netherlands). Temperature was controlled to within 1°C in each cat and ranged among cats from 36.1 to 38.2°C.

All signals were recorded on polygraphs and processed by a PDP 11/23 minicomputer (sample frequency, 100 Hz). Tidal volume, breathing frequency, ventilation ( $\dot{V}_I$ ), and end-tidal carbon dioxide and oxygen were determined using the minicomputer and stored on a breath-by-breath basis. For monitoring purposes during the experiment, averages for 20 breaths of ventilation, end-tidal gas tensions, and arterial pressure were calculated, displayed on a monitor, and stored on computer disk.

### Experimental Design

In each cat, the hypercapnic and hypoxic ventilatory responses were measured before and after the intravenous administration of 0.15 mg/kg morphine hydrochloride. Morphine studies were performed from about 30 min after the administration when ventilation had stabilized.

**Carbon Dioxide Studies.** Hypercapnic experiments consisted of  $P_{ET}CO_2$  challenges of approximately 7–10 mmHg during normoxia ( $P_{ET}O_2$  controlled at 110 mmHg). After a period of steady-state ventilation during which  $P_{ET}CO_2$  was slightly increased above resting values,  $P_{ET}CO_2$  was increased in a stepwise manner and kept constant for about 7 min. Thereafter, the  $P_{ET}CO_2$  was decreased to its original value and kept constant for another 7 min. In each cat, two or three control and two or three morphine studies were obtained. In the eight cats, we obtained 22 control and 21 morphine responses.

**Oxygen Studies.** In the hypoxic experiments, the  $P_{ET}O_2$  was forced according to the following pattern: 1) 300 mmHg, 2) 52 mmHg, 3) 113 mmHg, 4) 60 mmHg, 5) 42 mmHg, 6) 188 mmHg, and back to 300 mmHg. Each oxygen level was maintained for about 6 min. To be able to perform the hypoxic control and morphine studies at identical  $P_{ET}CO_2$  levels, the end-tidal carbon dioxide concentration was fixed at approximately 41 mmHg, which is about 6 mmHg higher than the normal

value in cats. Two control and two morphine studies were performed in each cat.

#### Data Analysis

**Oxygen Studies.** The hypoxic response of each cat was evaluated by taking mean values of ventilation and  $P_{ET}O_2$  of the last 20 breaths of each oxygen level. Using a least-squares method, ventilation was fitted to  $P_{ET}O_2$  according to the exponential function<sup>14</sup>:

$$\dot{V}_I = Ge^{-D \cdot P_{ET}O_2} + A \quad (1)$$

in which  $G$  is the overall hypoxic sensitivity,  $D$  is a shape parameter, and  $A$  is the ventilation during hyperoxia. Especially going from hyperoxia to hypoxia and when ventilation is depressed by morphine, several breaths are required before the target  $P_{ET}O_2$  was approached. Therefore, we only present results of the dynamics of the response for steps out of hypoxia, which can be performed more quickly. The ensemble average of the transitions from hypoxia to normoxia and to hyperoxia were determined by indexing on the time of the step change in  $P_{ET}O_2$  and with linear interpolation between breaths at 3-s intervals.

**Carbon Dioxide Studies.** The steady-state relation of ventilation to  $P_{ET}CO_2$  at constant  $P_{ET}O_2$  in the cat is linear down to the  $P_{ET}CO_2$  axis and well described by Berkenbosch *et al.*<sup>15</sup> and by DeGoede *et al.*<sup>16</sup>

$$\dot{V}_I = (S_p + S_c)(P_{ET}CO_2 - B) \quad (2)$$

The parameters  $S_c$  and  $S_p$  are the central and peripheral ventilatory carbon dioxide sensitivities, and the offset  $B$  represents the apneic threshold or extrapolated  $P_{ET}CO_2$  of the steady-state ventilatory response to carbon dioxide at zero ventilation.

To estimate  $S_c$ ,  $S_p$ , and  $B$ , we used the dynamic response of the ventilation and a two-compartment model as described previously.<sup>1,12</sup> We estimated all the parameters of the model simultaneously by fitting the data of each carbon dioxide study with a least-squares method.

#### Statistical Analysis

To compare the control and morphine group, we performed a paired *t* test on the parameters of the oxygen response. An analysis of variance with a two-way layout using a fixed model was performed on the estimated parameters of all the individual carbon dioxide studies. The level of significance was set at 0.05.

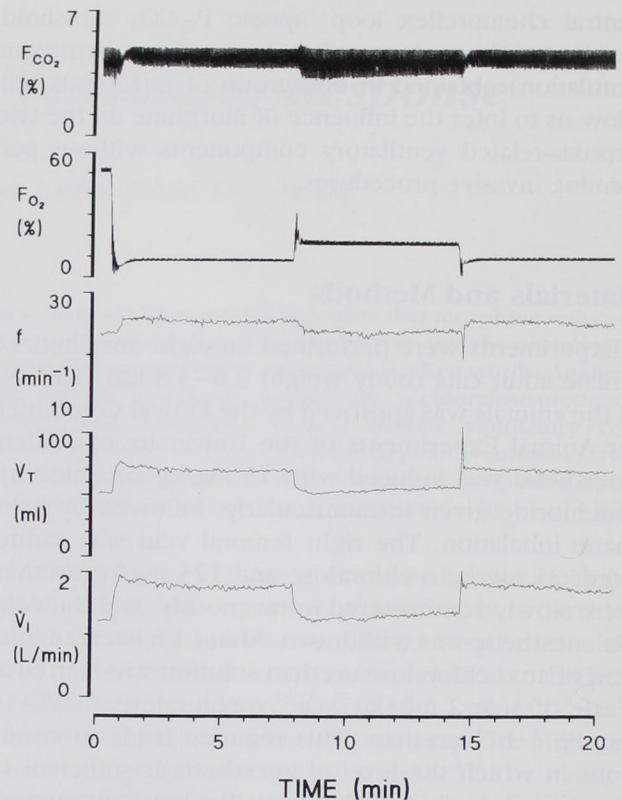


Fig. 1. Recording of part of an oxygen study. Plotted against time are ventilation ( $\dot{V}_I$ ), tidal volume ( $V_T$ ), breathing frequency ( $f$ ), and oxygen and carbon dioxide concentrations ( $FO_2$  and  $FCO_2$ , respectively) in tracheal gas.

## Results

### Oxygen Studies

Figure 1 shows the recording of a step transition from hyperoxia to hypoxia and back to normoxia. It took several breaths before the target hypoxic  $P_{ET}O_2$  was reached. The ventilatory response shows nearly no overshoot. The transition from hypoxia to normoxia occurs within two or three breaths. Nevertheless, the ventilatory response is relatively slow and shows a slight undershoot. Not all cats respond with a clear over- or undershoot in the response. In this sample of cats, we found a manifest over- or undershoot in two cats. In figure 2, the ensemble average of the responses from hypoxia to normoxia and to hyperoxia is shown. It shows that although the step out of hypoxia occurs in about 6 s, the ventilatory response is relatively slow. The control responses show a slight undershoot, which was no longer visible after administration of morphine.

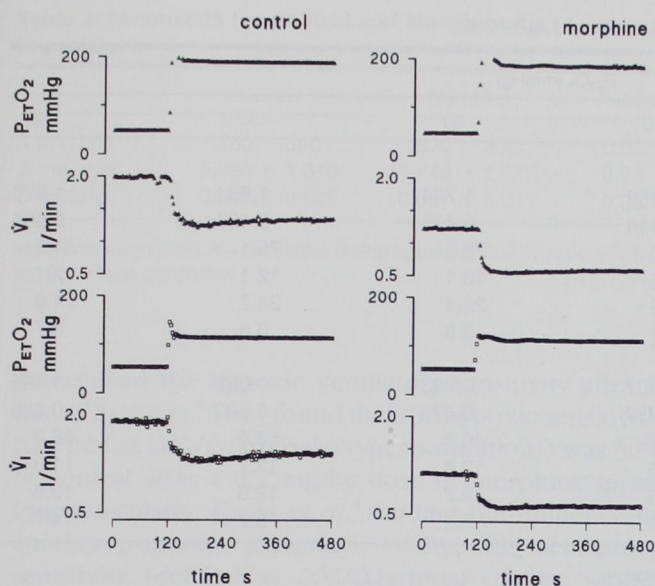
$\dot{V}_I$ , HYPOXIA, AND MORPHINE

Fig. 2. Ensemble average of ventilation ( $\dot{V}_I$ ) and end-tidal oxygen tension ( $P_{ET,O_2}$ ) of control and morphine studies for the transitions from hypoxia (52 mmHg) to normoxia (lower) and from hypoxia (42 mmHg) to moderate hyperoxia (upper).

Figure 3 shows a representative example of the steady-state ventilatory response curves to oxygen of one cat. It illustrates the general finding that after mor-

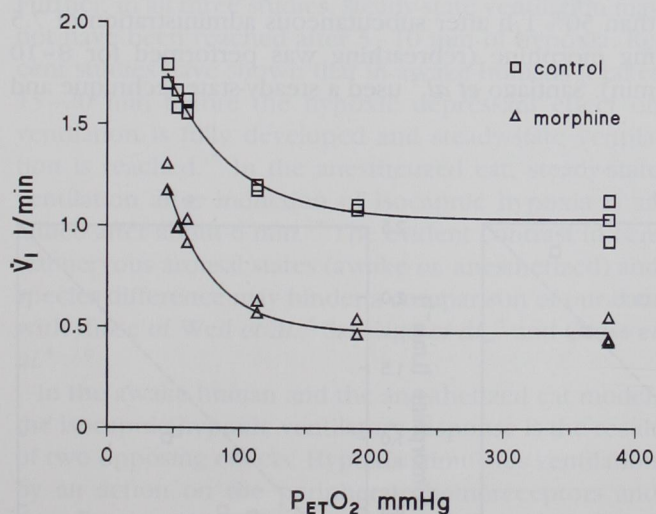


Fig. 3. Steady-state hypoxic ventilatory response curves during control (solid square) and after administration of morphine ( $\delta$ ) of one cat. The drawn lines are the exponentials fitted to the data according to the function  $\dot{V}_I = G \cdot \exp(-D \cdot P_{ET,O_2}) + A$ , with  $G = 1.807$  l/min,  $D = 0.0204$  mmHg $^{-1}$ , and  $A = 1.032$  l/min for control and  $G = 2.697$  l/min,  $D = 0.0291$  mmHg $^{-1}$ , and  $A = 0.474$  l/min for morphine.

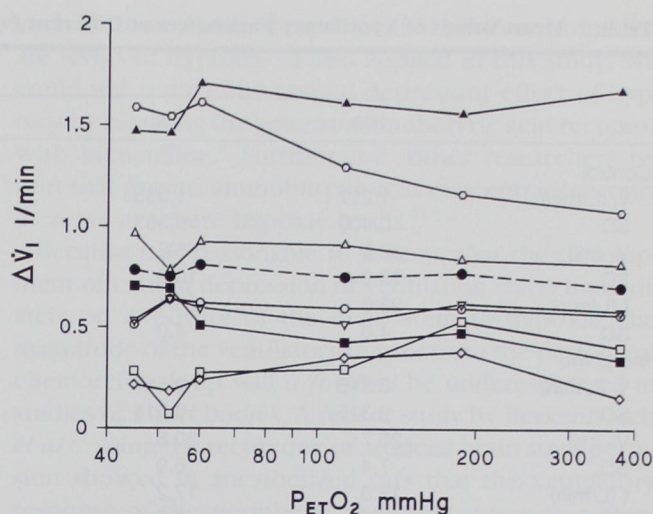


Fig. 4. Semilog plot of the difference in ventilation ( $\Delta\dot{V}_I$ ) between control and morphine experiments of each cat against end-tidal oxygen tension. Mean values are indicated by closed circles connected with a dotted line.

phine administration, hyperoxic ventilation is significantly depressed. However, the increase in ventilation by hypoxia is about the same, so that the response is approximately parallel and displaced to lower ventilation levels. This is also illustrated by figure 4, which shows the difference in ventilation ( $\Delta\dot{V}_I$ ) between control and morphine experiments at each oxygen level of all cats. Analysis of variance revealed that  $\Delta\dot{V}_I$  was not significantly different at each  $P_{ET,O_2}$  level ( $P = 0.65$ ). The mean steady-state ventilation and its components tidal volume and breathing frequency are shown in table 1. In figure 5, scatter diagrams of the hypoxic sensitivity (A), the shape parameter (B), and the ventilation at hyperoxia (C) are shown. The mean of the estimated parameters of the fits to equation 1 are summarized in table 2. Only the ventilation at hyperoxia (parameter A) decreased significantly from  $1,260 \pm 140$  ml/min to  $530 \pm 110$  ml/min.

#### Carbon Dioxide Studies

Twenty-two control studies and 21 morphine studies were obtained. Administration of morphine shifted the carbon dioxide response curve to higher end-tidal carbon dioxide values and decreased the slope (*i.e.*, total ventilatory carbon dioxide sensitivity [ $S_{TOT}$ ]). The value of parameter B increased significantly after morphine by approximately 6 mmHg (table 3). The central ( $S_c$ ) and peripheral ( $S_p$ ) carbon dioxide sensitivities de-

Table 1. Mean Values of Ventilatory Parameters at Different  $P_{ET}O_2$  Levels of Eight Cats

	$P_{ET}O_2$ (mmHg)					
	300	188	113	60	52	42
Control						
$\dot{V}_I$ (L/min)	1.217	1.330	1.358	1.744	1.834	1.979
SD	0.409	0.383	0.414	0.495	0.464	0.504
$V_T$ (ml)	52.5	56.6	58.0	72.5	75.1	81.5
SD	13.0	10.6	11.6	13.1	12.1	12.1
f (L/min)	23.0	23.4	23.2	23.8	24.2	24.0
SD	4.0	4.0	4.1	3.8	3.6	3.7
Morphine						
$\dot{V}_I$ (L/min)	0.516	0.557	0.607	0.933	1.082	1.195
SD	0.315	0.311	0.357	0.479	0.503	0.468
$V_T$ (ml)	28.7	30.8	32.7	46.3	53.0	58.7
SD	7.4	6.9	8.3	12.6	12.1	11.3
f (L/min)	17.0	17.2	17.5	19.2	19.6	19.8
SD	6.0	5.8	5.9	5.1	5.2	4.7

$\dot{V}_I$  = ventilation;  $V_T$  = tidal volume; f = breathing frequency; SD = standard deviation.

creased by about 30%, causing the ratio of  $S_p$  to  $S_c$  not to differ between treatments. Mean values of the parameters are collected in table 3.

## Discussion

Our study in anesthetized cats showed that although morphine depressed hyperoxic ventilation significantly by about 60%, the increase in ventilation due to isocapnic hypoxia was not diminished. This is reflected by the finding that the hypoxic sensitivity and the shape

parameter are not significantly changed (table 1). Comparative data from the literature are scarce. Weil *et al.*<sup>3</sup> and Santiago *et al.*<sup>5</sup> investigated the effects of morphine in awake humans. They consistently found a diminished response to hypoxia. Using a rebreathing technique, Weil *et al.*<sup>3</sup> observed a reduction of the hypoxic ventilatory sensitivity (defined by the shape parameter H of the hyperbolic function  $V_E = H \cdot [P_{ET}O_2 - 32]^{-1}$ ) by more than 50% 1 h after subcutaneous administration of 7.5 mg morphine (rebreathing was performed for 8-10 min). Santiago *et al.*<sup>5</sup> used a steady-state technique and

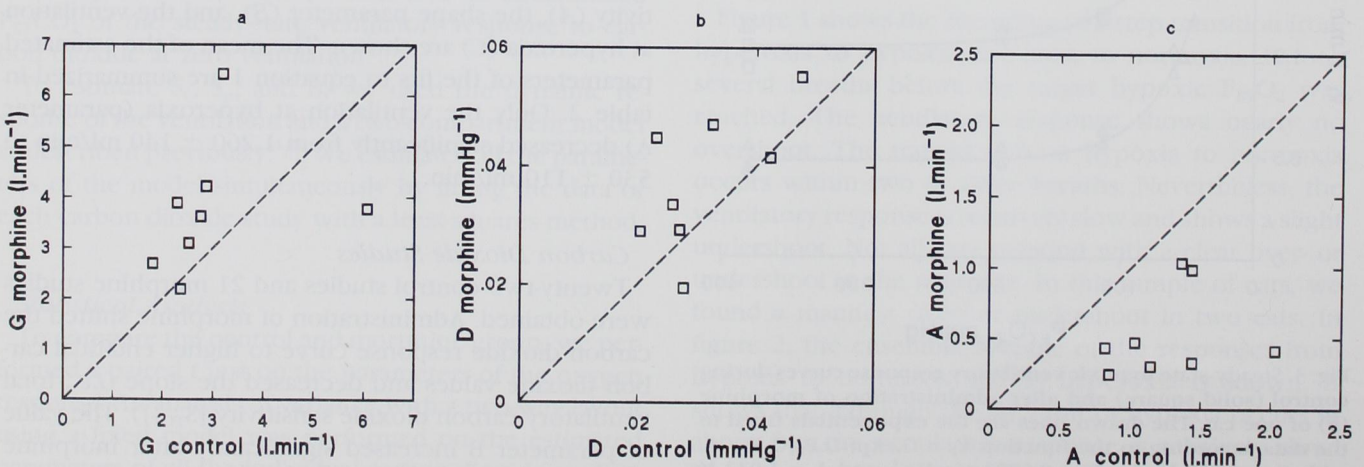


Fig. 5. Scatter diagrams of the parameters of the oxygen response curves. (A) Hypoxic sensitivity G. (B) Shape parameter D. (C) Ventilation at hyperoxia A. The dotted lines represent the lines of identity.

$\dot{V}_I$ , HYPOXIA, AND MORPHINE**Table 2. Parameters for Control and Morphine O<sub>2</sub> Experiments**

	Control	Morphine	P Value
A (ml · min <sup>-1</sup> )	1,260 ± 390	530 ± 308	0.002
G (ml · min <sup>-1</sup> )	2,980 ± 1,310	3,740 ± 1,276	0.22
D (mmHg <sup>-1</sup> )	0.031 ± 0.009	0.037 ± 0.011	0.08

Values are mean ± SD; A = ventilation during hyperoxia; G = hypoxic sensitivity; D = shape parameter.

determined the hypoxic ventilatory sensitivity after 5 min of hypoxia.<sup>5</sup> They found that the hypoxic sensitivity (defined as  $\Delta V_I/\Delta$ [arterial oxygen saturation]) was 30% of control after a 0.2 mg/kg dose of morphine given intramuscularly. Gross *et al.*<sup>4</sup> studied the influence of another  $\mu$ -agonist, alfentanil, on hypoxic ventilatory sensitivity (defined as  $\Delta V_I/\Delta$ [arterial oxygen saturation]; oxygen saturation was decreased to about 70% for 2 or 3 min). They observed a reduction of 20% of the hypoxic sensitivity during alfentanil administration. As indicated in these studies, different procedures to measure the ventilatory response to hypoxia were used. The results of these studies are difficult to interpret and to compare with our data for other reasons, too. In the studies of Weil *et al.*<sup>3</sup> and Santiago *et al.*,<sup>5</sup> the end-tidal or arterial PCO<sub>2</sub> in the morphine studies was higher compared with control studies (more than 2–5 mmHg). Further, in all three studies, steady-state ventilation may not have been reached after 5–10 min of hypoxia. Recent studies have shown that in awake humans it takes 15–20 min before the hypoxic depressant effect on ventilation is fully developed and steady-state ventilation is reached.<sup>17</sup> In the anesthetized cat, steady-state ventilation after induction of isocapnic hypoxia is attained after about 6 min.<sup>18</sup> The evident contrast in central nervous arousal states (awake *vs.* anesthetized) and species difference may hinder a comparison of our data with those of Weil *et al.*,<sup>3</sup> Santiago *et al.*,<sup>5</sup> and Gross *et al.*<sup>4</sup>

In the awake human and the anesthetized cat model, the isocapnic hypoxic ventilatory response is the result of two opposing effects: Hypoxia stimulates ventilation by an action on the peripheral chemoreceptors and depresses ventilation *via* an effect within the central nervous system.<sup>6–8</sup> The depressant effect of hypoxia in the anesthetized cat is related to an increased wash-out of acid metabolites from the brain compartment due to an increase in brain blood flow<sup>8,19,20</sup> and probably also to the release or synthesis of inhibiting neurotransmitters

such as gamma-aminobutyric acid.<sup>9</sup> However, at moderate levels of hypoxia, as also applied in this study, we could not reduce the central depressant effect of hypoxia by blocking the gamma-aminobutyric acid receptor with bicuculline.<sup>8</sup> Furthermore, other researchers report that gamma-aminobutyric acid concentrations only increase at severe hypoxic levels.<sup>21</sup>

Because it is reasonable to assume that the development of central depression of ventilation starts immediately on exposure of the brain stem to hypoxia, the magnitude of the ventilatory output from the peripheral chemoreflex loop will *a fortiori* be underestimated in studies of intact bodies. A recent study by Berkenbosch *et al.*<sup>22</sup> using the technique of artificial brain stem perfusion showed in anesthetized cats that the ventilatory response of the peripheral chemoreceptors to a stepwise change in P<sub>ET</sub>-O<sub>2</sub> contains a fast and a slow component.<sup>14</sup> In humans, with the termination of a 1-min hypoxic episode, ventilation also shows a fast and a slow component.<sup>22</sup> The existence of this slow component in the anesthetized cat explains the variability that is commonly observed in the time course of the overall hypoxic ventilatory response.<sup>14</sup> Depending on the magnitude and time constant, the slow component of the peripheral chemoreceptor response can mask the central depressant effect of hypoxia, preventing a biphasic appearance of the response. This was the case in six of the cats in this study. This indicates that separation of the measured hypoxic ventilatory responses into peripheral and central components is impossible from studies in intact animals. Because the overall hypoxic sensitivity (parameter G in equation 1) estimated in our study is the result of the two opposing effects of hypoxia (peripheral stimulating and central depressant), it provides little or no information on if and how morphine affected either of these.

**Table 3. Parameters for Control and Morphine CO<sub>2</sub> Experiments in Eight Cats**

	Control	Morphine	P Value
No. of runs	22	21	
B (mmHg)	25.9 ± 5.7	32.1 ± 4.4	<0.0001
S <sub>TOT</sub> (ml · min <sup>-1</sup> · mmHg <sup>-1</sup> )	93.9 ± 41.3	68.1 ± 35.6	<0.0001
S <sub>c</sub> (ml · min <sup>-1</sup> · mmHg <sup>-1</sup> )	81.0 ± 37.7	59.6 ± 33.0	<0.0001
S <sub>p</sub> (ml · min <sup>-1</sup> · mmHg <sup>-1</sup> )	12.7 ± 7.0	8.5 ± 4.0	0.012
S <sub>p</sub> /S <sub>c</sub>	0.165 ± 0.105	0.161 ± 0.084	0.85

Values are means ± SD; B = apneic threshold; S<sub>c</sub> = ventilatory carbon dioxide sensitivity of the central chemoreflex loop; S<sub>p</sub> = ventilatory carbon dioxide sensitivity of the peripheral chemoreflex loop; S<sub>TOT</sub> = S<sub>c</sub> + S<sub>p</sub>.

To increase our understanding of how morphine influenced the hypoxic ventilatory response, we used the results obtained in carbon dioxide studies. Our carbon dioxide studies showed, corresponding to an earlier study in anesthetized cats,<sup>1</sup> that the main depressant effect of morphine on ventilation was by an effect on the apneic threshold. Due to this increase in apneic threshold, we had to perform the control oxygen studies at a relative hypercapnic  $P_{ET}CO_2$ . The peripheral and central carbon dioxide sensitivities were depressed by an equal percentage (approximately 30%). As a consequence, the ratio of these sensitivities ( $S_p/S_c$ ) did not differ in the treatments (table 2). Previously we reasoned that the change in apneic threshold we observed was not due to an effect of morphine on the chemoreceptors themselves, although we cannot entirely exclude such an effect.<sup>1</sup> The finding that the peripheral and central carbon dioxide sensitivities are depressed to the same extent supports the idea that the depressant effect of morphine is mainly on the neuronal structures common to the peripheral and central chemoreflex pathway; that is, the respiratory centers within the brain stem rather than the peripheral and central chemoreceptors per se. Because signals from the peripheral chemoreceptors due to hypoxia and hypercapnia are transported to the brainstem *via* identical pathways, we would expect, based on our carbon dioxide studies, that the response of the peripheral chemoreflex loop to hypoxia also will be depressed by morphine. We cannot exclude the possibility that the peripheral carbon dioxide sensitivity is depressed somewhat more than the peripheral hypoxic sensitivity by morphine. This is explained by an effect of morphine on peripheral carbon dioxide sensitivity at hyperoxia, which is an appreciable part of the total peripheral normoxic carbon dioxide sensitivity in the anesthetized cat.<sup>15</sup>

Our remarkable observation that the overall hypoxic sensitivity is not diminished suggests that the counteracting central depressant effect of hypoxia was lessened by morphine. This may be due to a diminished synthesis or release of inhibiting neuromodulators. However, we believe that in anesthetized cats the depressant effect of moderate hypoxia on ventilation is due to an increase in brain blood flow.<sup>8,19</sup> Our results then suggest that morphine reduces brain blood flow reactivity to hypoxia at constant  $P_{ET}CO_2$ . Morphine decreases resting brain blood flow coupled to a reduction of brain metabolism.<sup>24</sup> To the best of our knowledge, no data are available on the influence of morphine on brain blood flow reactivity to isocapnic hypoxia.

Do our data apply to humans, and if so, what is their clinical importance? There are now several examples of striking similarities between feline and human ventilatory responses to isocapnic hypoxia in the awake and anesthetized states (for example, see references 8 and 23). Not only do the responses appear similar in shape, but the underlying mechanisms (peripheral stimulation and central depression) probably have identical origins. It is interesting to note that the central nervous system arousal states (*i.e.*, awake *vs.* anesthetized or sedated) are more important in causing differences in the response shape and mechanisms than are species differences.<sup>8</sup>

Application of our results to anesthetized (or sedated) persons breathing spontaneously then suggests that intravenous morphine reduces hyperoxic, normoxic, and hypoxic ventilation. The ability of the respiratory control system to increase ventilation in response to imposed hypercapnic loads is reduced but not abolished. Evidently, patients will remain (or resume) breathing only if their resting  $P_{ET}CO_2$  is above the apneic threshold, which in our study was increased by about 25%. The ventilatory response to hypoxia would be altered by morphine in the sense that steady-state hypoxic sensitivity will remain identical to control, but the level of ventilation is diminished at all  $PO_2$  levels.

Obviously, several caveats should be stated before extrapolating our results to humans. First, all agents used for general anesthesia or sedation affect ventilatory control, and an interaction between these drugs and opioids also may occur.<sup>24,25</sup> Although the general anesthetic used in our preparation ( $\alpha$ -chloralose-urethan) does not seem to affect resting  $P_{ET}CO_2$  and the slope of the carbon dioxide response curve compared with the awake cat,<sup>10,11</sup> an interaction of this particular anesthetic regimen (or the central nervous system arousal state it induces) and morphine is not unlikely. Second, during and after surgery, additional respiratory drives (noxious stimulation, shivering, verbal, and tactile stimulation by recovery room personnel) play an important role in the balance between respiratory depression and stimulation.<sup>26</sup> Third, we successfully opened the feedback loop with the dynamic end-tidal forcing technique. In patients, the feedback loop remains intact, and variations in  $P_{ET}CO_2$  occur due to morphine alone or due to ventilatory responses. If we take this into account, our conclusions about the effect of morphine on ventilatory control as well as the mechanisms involved are valid for anesthetized cats and probably also for humans. However, extrapolation of our results to the periopera-

tive setting should be made with caution because several factors that we have not studied should be considered.

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